GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 11 (368) ноябрь 2025

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
NO 11 (368) 2025

Содержание:

GEORGIAN MEDICAL NEWS
No 11 (368) 2025

THE PROTECTIVE EFFECT OF MILK OF THISTLE AGAINST DOXORUBICIN OR METHOTREXATE INDUCED CARDIOTOXICITY

Shamil H. Othman[1]*, Ahmed Abdulsallam[2], Musab Mohammed Khalaf[3].

[1]*Department of Pharmacology, College of Medicine, University of Mosul, Mosul, Iraq.*

[2]*Department of Pharmacy Techniques, Mosul Medical Technical Institute, Northern Technical University, Mosul, Iraq.*

[3]*Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq.*

Abstract.

Background: Doxorubicin (DOX) and methotrexate (MXT) are strong anticancer agents and gold standard therapy for several malignancies, with efficacy restricted by cardiotoxicity. Milk thistle extract (MTE) has demonstrated strong antioxidant and cytoprotective properties; we sought to determine the role of MTE in protection against Dox or MXT-induced cardiac damage.

Methods: A total of 35 white albino rats were divided into five groups: control, Dox alone (1.66mg/kg/48hr, IP) group, MXT alone (oral 0.5mg/kg/48hr, oral) group, Dox+MTE group (1.66mg/kg/48hr Dox IP+150mg/kg/day MTE oral), and MXT+MTE (0.5mg/kg/48hr MXT oral +150mg/kg/day MTE oral) group. The duration of experiment were seven days. A histopathological examination was done at the end of experimentation.

Results: Dox and MXT use in the rat model has induced severe cardiotoxicity with inflammatory cell infiltration, structural damage of cardiac tissue, and morphological changes. Milk thistle pretreatment extensively saved cardiac architecture.

Conclusions: MTE use with Dox or MXT demonstrated marked cardioprotection potential via reduced inflammatory cell infiltration and cardiac tissue protection, suggesting that MTE could potentially emerge as a valuable tool to block cardiac complications in Dox- or MXT-treated patients.

Key words. Doxorubicin, methotrexate, milk thistle extract, cardiotoxicity, chemotherapy.

Introduction.

Doxorubicin (DOX) and methotrexate (MXT), considered as the most popular and strong chemotherapeutic agents in clinical settings for the treatment of oncology, via their efficacy against a wide range of malignancies (e.g. breast cancer, lymphomas, sarcomas, and acute leukemia), significantly enhance survival quality for cancer patients [1,2]. Nonetheless, the indication of these anticancer agents is severely restricted by their cardiotoxic adverse effects, which can present as acute cardiac dysfunction, chronic cardiomyopathy, and eventually congestive heart failure [2].

The mechanism of cardiotoxicity is complex, involving the generation of reactive oxygen species (ROS), lipid peroxidation, mitochondrial dysfunction, DNA damage, and perturbation of calcium homeostasis inside cardiomyocyte [3,4]. Dox has a high affinity for cardiolipin, mitochondrial membranes' phospholipid, which leads to accumulation in heart tissue, resulting in oxidative stress and hence progressive myocardial damage [5-7]. Moreover, doxorubicin hinders iron metabolism, enhancing the production of doxorubicin-iron complexes that catalyze free radical production through Fenton reactions, further worsening cardiac injury [8,9]. While methotrexate induces cardiac injury through a cascade of biochemical destruction that starts with its blocking of dihydrofolate reductase [10], leading to blocking the conversion of dihydrobiopterin to tetrahydrobiopterin, and also uncoupling nitric oxide synthase leading to increased apoptosis induced by T cells and mitigating the immune response [11].

The need for a cardioprotective agent that can mitigate anticancer-induced cardiac toxicity without compromising anticancer efficacy has directed research into natural compounds with cardioprotective impacts, including milk thistle (Silybum marianum), due to its antioxidant, anti-inflammatory, and cytoprotective properties. The present study aimed to assess the cardioprotective role of milk thistle extract (MTE) against doxorubicin or methotrexate-induced cardiotoxicity by examining histopathological changes.

Materials and Methods.

Study design: The study was ethically approved by the College of Medicine (University of Mosul, Iraq), Ref: Session 30 on 06 October 2025. The experimental part on laboratory animals was conducted in the animal house utility of the College of Veterinary Medicine (University of Mosul, Iraq). A total of 35 rats (age, 10 weeks old; weight, 200 grams) were kindly provided by the animal house utility at the College of Veterinary Medicine for use in this study. These rats were adapted for 2 weeks and handled under standard conditions of light/dark cycle, temperature, and humidity, with free access to food and water.

Experimental design:

The 35 rats were subdivided into 5 groups:

C=Control group (7 rats): were administered normal saline (orally, 7 days).

Dox = Doxorubicin group (7 rats): received Dox IP at a dose of 1.66mg/kg every other day.

MXT=Methotrexate group (7 rats): received MXT orally at a dose of 0.5mg/kg every other day.

Dox+MTE = Doxorubicin and milk thistle group (7 rats): received Dox IP at a dose of 1.66mg/kg every other day with milk thistle at an oral dose of 150mg/kg/day, for 7 days.

MXT+MTE = Methotrexate and milk thistle group (7 rats): received MXT orally at a dose of 0.5mg/kg every other day with milk thistle at an oral dose of 150mg/kg/day, for 7 days.

Drug preparation:

Drugs have been freshly prepared in the laboratory and given to animals orally by gavage needle and IP by syringe needles. Doxorubicin inj (Doxo-cell 50 mg, Stadapharm Gmbh

(Germany)) was diluted for administration using normal saline. Milk thistle extract (300mg, NOW Foods (USA)) and MXT (2.5 mg, EbewePharma (Austria)) for administration.

Histological examination:

Rats were sacrificed at the end of the experiment by cervical dislocation under deep anesthesia. The heart tissues were harvested from rats in each group and thoroughly rinsed with normal saline and fixed in 10% buffered formalin for a few days at room temperature until ready for processing. Tissue processing for slide preparation started with alcohol dehydration by exposure to graded alcohol to ensure complete dehydration, followed by clearing at the end by impregnation in xylene (twice, 1 hour each) to remove alcohol, to be ready for paraffin embedding and molded in embedding cassettes. The formed paraffin blocks were sectioned using a rotary microtome at 4-5µm thickness [12]. The slices were placed over slides and then deparaffinized and rehydrated to be ready for staining with hematoxylin and eosin (H&E), moreover, oil red o staining for lipid was used for Dox alone group to stain deposited lipid. All slides were examined by light microscopy using a digital camera system.

Results.

Control group:

The heart tissue sections from control group rats, showing intact cardiac muscle, demonstrating parallel organization of muscle fibers in a striated manner. Interstitial spaces inside cardiac muscle fiber showed scattered mild lymphocytic infiltration (Figure 1).

Dox group:

Cardiac muscle tissue demonstrated vascular congestion throughout the myocardium with lymphocytes dispersed between the muscle fibers. The cardiac myocytes showed disrupted striated shape due to the inflammation and congestion (Figure 2A). Adjacent to the cardiac tissue, a hibernating or dormant fatty tissue is noted, forming a characteristic contrast with the striated heart muscle (Figure 2B).

MXT group:

Cardiac muscle characterized by disrupted cardiac striated organization with vacuolation, alongside severe lymphocytic inflammation throughout the interstitial spaces between muscle fires (Figure 3).

Cardiac muscle characterized by disrupted cardiac striated organization with vacuolation, disrupted longitudinal bundles, fragmented tissues, alongside severe lymphocytic inflammation throughout the interstitial spaces between muscle fires (Figure 4).

MXT+MTE group:

The cardiac muscle demonstrated a striated shape with fibers arranged in parallel bundles running in different directions. The interstitial spaces between muscle bundles demonstrated slight changes, with mild lymphocyte infiltration and slight vessel congestion (Figure 5).

The muscle fibers presented with their normal striated pattern with slightly congested capillaries within the tissue, alongside mild lymphocyte accumulation between the muscle fibers (Figure 6).

Dox+MTE:

The cardiomyocyte appeared with their striated longitudinal bundles, with severe blood vessel congestion, severe scattered lymphocytic infiltration within muscle layers (Figure 7).

The muscle fibers preserved their striated appearance pattern and are arrayed in organized bundles arranged longitudinally across the field, and slightly dilated blood vessels and capillaries appeared between the muscle fibers. The cardiac myocytes maintained their structural integrity with visible nuclei and well-defined cell boundaries. The interstitial spaces appear mildly expanded, consistent with the described congestion (Figure 8).

Summarized the histopathological outcome:

MTE has protected the cardiac valve from abnormalities compared to Dox or MXT alone, moreover, Dox or MXT have moderate to severe focal lymphocytic infiltration in valve tissue and acquired abnormal cartilage metaplasia, it reflects structural damage and remodelling processes.

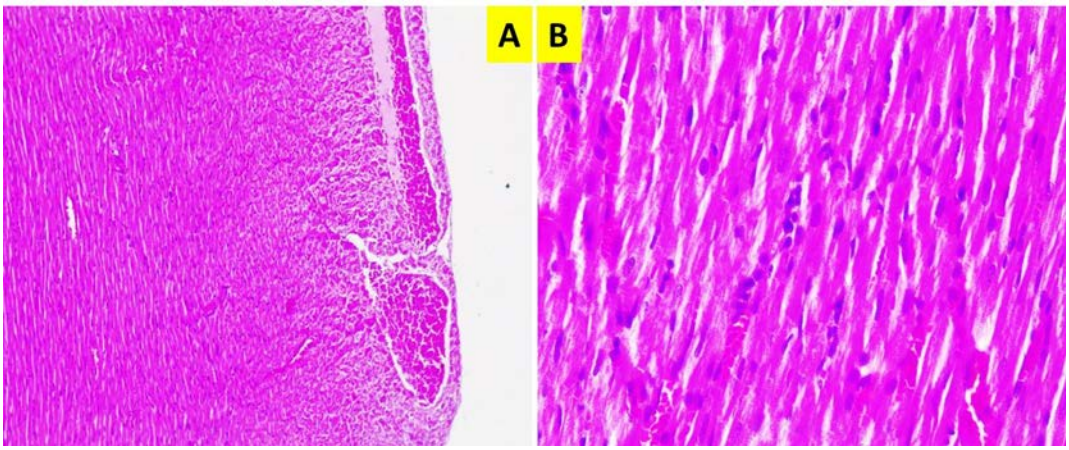

Figure 1. *Photomicrograph of the heart section from rats in the control group showing (A) heart muscle with vessels (H&E; x100), (B) heart muscle with mild lymphocytic infiltration between muscle fibers (H&E; x400).*

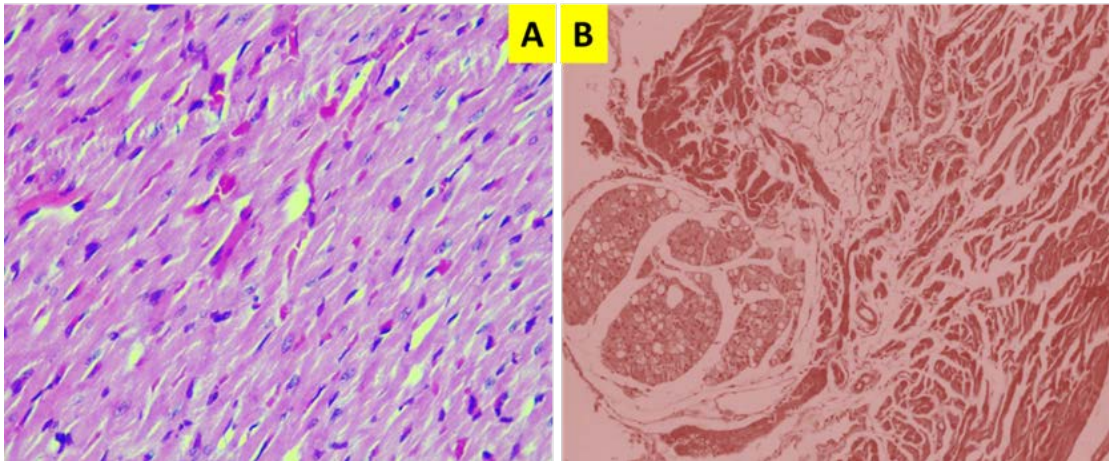

Figure 2. *Photomicrograph of the heart section from rats in the Dox group showing heart muscle with severe congestion & extensive lymphocytes between muscle fibers (H&E; x400). (B) Heart muscle with adjacent hibernating fat tissue (Oil red O; x100).*

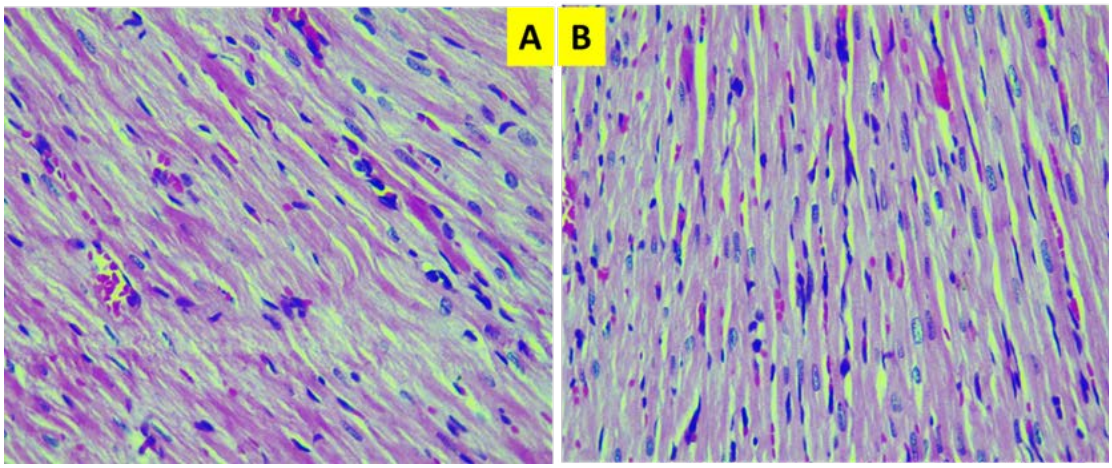

Figure 3. *Photomicrograph of the heart section from rats in the MXT group showing (A) heart muscle with slightly disrupted striated architecture (H&E; x400), (B) heart muscle with severe lymphocytic inflammation between muscle fibers (H&E; x400).*

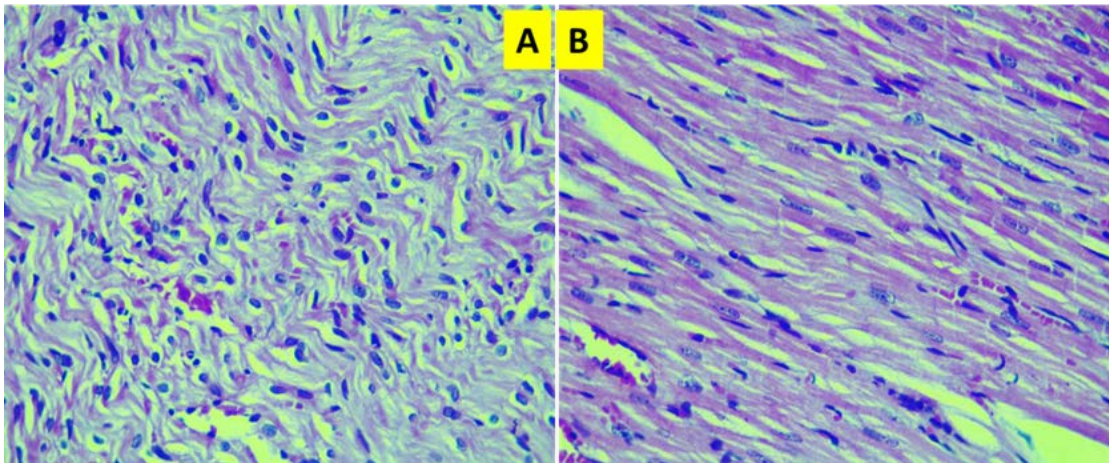

Figure 4. *Photomicrograph of the heart section from rats in the MXT group showing. A) heart muscle with severe lymphocytic inflammation between muscle fibers (H&E; x400). (B) heart muscle with clear lymphocytes infiltration between muscle fibers (H&E; x400).*

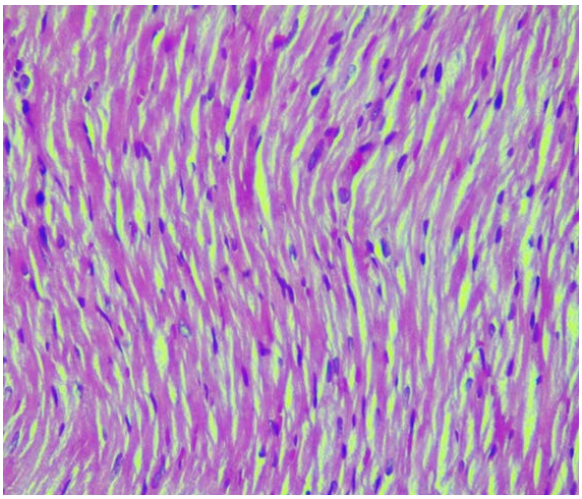

Figure 5. *Photomicrograph of the heart section from rats in the MXT+MTE group showing heart muscle with no significant changes (H&E; x400).*

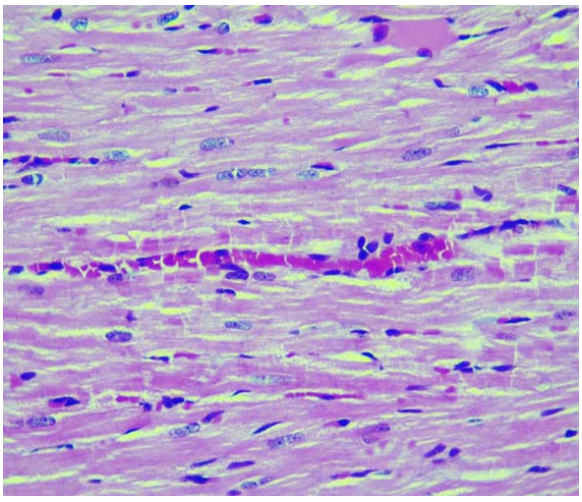

Figure 6. *Photomicrograph of the heart section from rats in the MXT+MTE group showing heart muscle with slight congestion & mild lymphocytic inflammation between muscle fibers (H&E; x400).*

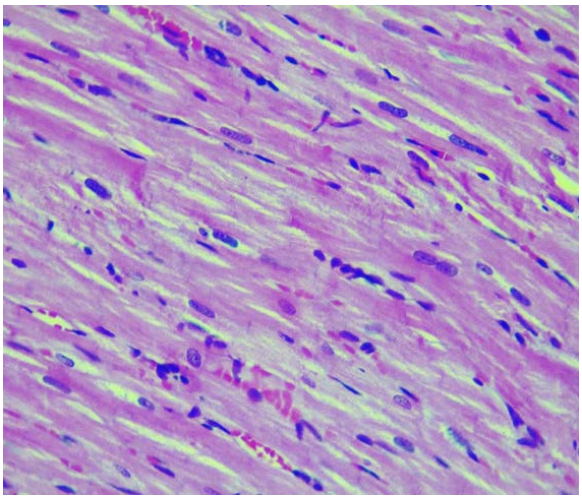

Figure 7. *Photomicrograph of the heart section from rats in the Dox+MTE group showing heart muscle with slight congestion & mild lymphocytic inflammation between muscle fibers (H&E; x400).*

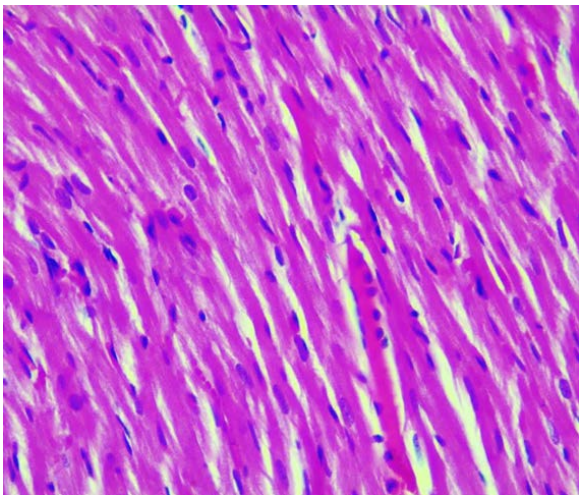

Figure 8. *Photomicrograph of the heart section from rats in the Dox+MTE group showing heart muscle with mild congestion (H&E; x400).*

Table 1. *Summarized outcome of the processed tissues in the studied groups.*

Tissue parts		**C**	**Dox**	**MXT**	**MXT+MTE**	**Dox+MTE**
Cardiac muscle	**Muscle fiber necrosis**	Negative	Sever necrosis	Moderate necrosis	Weak necrosis	Moderate necrosis
	Nuclei	No changes	No changes	Slight changes	No changes	No changes
	Intracardiac Capillary Vessels	Normal	Sever congestion	Moderate congestion	Mild congestion	Moderate congestion
	Cells infiltrate: Lymphocytes	Mild	Sever	Sever	Mild	Sever
	Cells infiltrate: Neutrophils	Negative	positive	positive	Negative	positive
	Cells infiltrate: eosinophils	Negative	Negative	Negative	Negative	Negative
Valve changes	**Lymphocytic infiltrate**	Negative	Sever focal	Moderate focal	Mild focal	Mild focal
	Abnormal tissue	Negative	Cartilage metaplasia	Cartilage metaplasia	Cartilage metaplasia	Cartilage metaplasia
Subpericardial fat	**Inflammatory cells**	Very slight immune cells present	Severe Infiltration	Severe Infiltration	Moderate Infiltration	Severe Infiltration

MTE has no role in changing the nuclear morphology, correspondingly, both groups showed mild congestion of intracardiac capillary vessels, reflecting that MTE protective effects are limited to the heart rather than the vessels.

Discussion.

The present study confirmed that MTE has provided cardioprotection against Dox or MXT in the rat model, as confirmed by histological changes induced by Dox or MXT and blocked by MTE. The histopathological findings of diminished cardiomyocyte injury offered morphological confirmation of MTE protective effects at the histological level. The reduced rate of myofibrillar interruption, cytoplasmic vacuolization, and nuclear disruption revealed in Dox- or MXT-exposed animals reflects that MTE defends against the direct cytotoxic effects of Dox or MXT on cardiac muscle cells. The protection of intercalated disc integrity and protection of normal sarcomere organization imply that MTE defends not only individual cardiomyocytes but also the structural architecture necessary for integration of cardiac contraction. This marked cellular protection is important for blocking both acute cardiac malfunction and the continuous architecture remodelling that discriminates chronic anthracycline cardiomyopathy.

The anti-inflammatory effects of MTE contribute notably in its overall cardioprotective profile [13-15]. The histopathological study revealed markedly mitigated inflammatory cell infiltration and decreased expression of pro-inflammatory markers in cardiac tissue in MTE-treated rats [1,16,17]. This outcome is congruent with recognized actions of MTE ability to alter inflammatory pathways, including nuclear factor-kappa B stimulation and intracellular cytokine production [18-21]. The blocking of inflammatory biomolecules is clinically related because chronic inflammation has a great role in the transition from acute cardiac injury to progressive heart failure; hence, MTE interrupts this inflammatory cytokine synthesis, providing cardiac damage [23,23].

The mechanism of action of MTE in providing protection against heart toxicity via antioxidant, anti-inflammatory, and cytoprotective activity [24-26]. These actions pertained to MTE have provided protection against anticancer-induced cardiotoxicity, whose primary cardiac toxicity effects are related

to oxidative stress, release of proinflammatory cytokine pools, and cardiac tissue damage [2,24].

The use of Dox in children's oncology is associated with a high cure rate but restricted by cardiotoxicity, so MTE provided cardioprotection [14,21,22]. This safety profile and well-documented tolerability profile enable clinical translation to potentiate the transfer of MTE directly to clinical settings. Assessing whether MTE impedes antitumor efficacy is a significant future objective [27,28].

Conclusion.

The study concluded that both Dox and MXT have shown cardiotoxicity effects, confirmed by damaged cardiac tissue structural components and infiltrated immune cells. The Extract of milk thistle has provided protection against either drugs by retaining the histological architecture of the heart tissue. Moreover, the extract has mitigated inflammatory infiltration in rat tissue in both cases.

REFERENCES

1. Abdelsalam HM, Samak MA, Alsemeh AE. Synergistic therapeutic effects of Vitis vinifera extract and Silymarin on experimentally induced cardiorenal injury: The pertinent role of Nrf2. Biomed Pharmacother. 2019;110:37-46.
2. Singh M, Kadhim MM, Turki Jalil A, et al. A systematic review of the protective effects of silymarin/silibinin against doxorubicin-induced cardiotoxicity. Cancer Cell Int. 2023;23:88.
3. Yin Y, Shen H. Advances in Cardiotoxicity Induced by Altered Mitochondrial Dynamics and Mitophagy. Front Cardiovasc Med. 2021;8:739095.
4. Varga ZV, Ferdinandy P, Liaudet L, et al. Drug-induced mitochondrial dysfunction and cardiotoxicity. Am J Physiol Heart Circ Physiol. 2015;309:H1453-67.
5. Wallace KB, Sardão VA, Oliveira PJ. Mitochondrial Determinants of Doxorubicin-Induced Cardiomyopathy. Circ Res. 2020;126:926-941.
6. Cappetta D, De Angelis A, Sapio L, et al. Oxidative Stress and Cellular Response to Doxorubicin: A Common Factor in the Complex Milieu of Anthracycline Cardiotoxicity. Oxid Med Cell Longev. 2017;2017:1521020.
7. Ito-Hagiwara K, Hagiwara J, Endo Y, et al. Cardioprotective strategies against doxorubicin-induced cardiotoxicity: A review from standard therapies to emerging mitochondrial transplantation. Biomed Pharmacother. 2025;189:118315.
8. Vitale R, Marzocco S, Popolo A. Role of Oxidative Stress and Inflammation in Doxorubicin-Induced Cardiotoxicity: A Brief Account. Int J Mol Sci. 2024;25.
9. Ichikawa Y, Ghanefar M, Bayeva M, et al. Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. J Clin Invest. 2014;124:617-630.
10. Nagy A, Börzsei D, Hoffmann A, et al. A Comprehensive Overview on Chemotherapy-Induced Cardiotoxicity: Insights into the Underlying Inflammatory and Oxidative Mechanisms. Cardiovasc Drugs Ther. 2024.
11. Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. Nature Reviews Rheumatology. 2020;16:145-54.
12. Abdullah SI, Al-Bayti AAH, Salih MJ, et al. Histological and Biochemical Changes Associated with Blocking of Serotonin Receptor. Trop J Nat Prod Res. 2022;6:1189-1192.
13. Kadoglou NPE, Panayiotou C, Vardas M, et al. A Comprehensive Review of the Cardiovascular Protective Properties of Silibinin/Silymarin: A New Kid on the Block. Pharmaceuticals (Basel). 2022;15.
14. Lindner E, Alhmouz MM, Abuhalimeh R, et al. Is Milk Thistle a Cardioprotective Ally or a Thrombotic Threat? JACC Case reports. 2025;30:104999.
15. Zhao Y, Zhou Y, Gong T, et al. The clinical anti-inflammatory effects and underlying mechanisms of silymarin. iScience. 2024;27:111109.
16. Hassaneen NH, Hemeda SA, El Nahas AF, et al. Post-treatment of rat aflatoxicosis by camel milk and silymarin. Front Pharmacol. 2025;16:1513105.
17. Alharbi FK. Silymarin alleviates diclofenac-induced hepatotoxicity in male Wistar rats: Histopathological investigation. Open Vet J. 2025;15:1790-7.
18. Karimi G, Vahabzadeh M, Lari P, et al. “Silymarin”, a promising pharmacological agent for treatment of diseases. Iran J Basic Med Sci. 2011;14:308-317.
19. Surai PF, Surai A, Earle-Payne K. Silymarin and Inflammation: Food for Thoughts. Antioxidants (Basel, Switzerland). 2024;13.
20. Kamel NM, El-Sayed SS, El-Said YAM, et al. Unlocking milk thistle’s anti-psoriatic potential in mice: Targeting PI3K/AKT/mTOR and KEAP1/NRF2/NF-κB pathways to modulate inflammation and oxidative stress. Int Immunopharmacol. 2024;139:112781.
21. Fallah M, Davoodvandi A, Nikmanzar S, et al. Silymarin (milk thistle extract) as a therapeutic agent in gastrointestinal cancer. Biomed Pharmacother. 2021;142:112024.
22. Neelab, Zeb A, Jamil M. Milk thistle protects against non-alcoholic fatty liver disease induced by dietary thermally oxidized tallow. Heliyon. 2024;10:e31445.
23. Jaffar HM, Al-Asmari F, Khan FA, et al. Silymarin: Unveiling its pharmacological spectrum and therapeutic potential in liver diseases-A comprehensive narrative review. Food Sci Nutr. 2024;12:3097-3111.
24. Razavi BM, Karimi G. Protective effect of silymarin against chemical-induced cardiotoxicity. Iran J Basic Med Sci. 2016;19:916-923.
25. Khazaei R, Seidavi A, Bouyeh M. A review on the mechanisms of the effect of silymarin in milk thistle (Silybum marianum) on some laboratory animals. Vet Med Sci. 2022;8:289-301.
26. Taleb A, Ahmad KA, Ihsan AU, et al. Antioxidant effects and mechanism of silymarin in oxidative stress induced cardiovascular diseases. Biomed Pharmacother. 2018;102:689-698.
27. Al-Hasnawi Z, Hasan HM, Abdul Azeez JM, et al. Cardioprotective strategies in the management of chemotherapy-induced cardiotoxicity: current approaches and future directions. Ann Med Surg. 2024;86:7212-7220.
28. Mir A, Badi Y, Bugazia S, et al. Efficacy and safety of cardioprotective drugs in chemotherapy-induced cardiotoxicity: an updated systematic review & network meta-analysis. Cardio-oncology (London, England). 2023;9:10.